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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/578,900	CARULLI ET AL.
Examiner	**Art Unit**
Jon Eric Angell	1635

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *3-5 and 8-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2,6,7 and 48-61* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/04;11/04*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 11/22/2004 has been entered.

Claims 1-61 are currently pending in the application and are addressed herein.

Claims 3-5 and 8-47 have withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim for the reasons of record. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/12/02.

Claims 1, 2, 6, 7 and 48-61 are examined herein.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 10/4/04 as well the IDS submitted on 11/22/04 are acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 52, 54-57 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is noted that claims 2, 52, and 54-57 all dependent on claim 1. Claim 2 recites the limitation "said molecule", claim 52 recites the limitation "the molecule which binds to HBM or Zmax1" and claims 54-57 recite the limitation "the molecule", all referring to a molecule in claim 1. It is noted that claim 1 reads "A method of identifying a molecule involved in lipid regulation comprising identifying a molecule that binds to, or that inhibits binding of a molecule to, HBM or Zmax1. It is unclear which molecule the instant claims are referring to. With respect to claim 52, it is noted that both "molecules" recited in claim 1 bind to HBM or Zmax1, therefore, it is unclear which "molecule which binds to HBM or Zmax1" the claim refers to.

Claim 61 reads, "The method of claim 1 further comprising the step of determining whether the molecule that binds to, or that inhibits binding of a molecule to, HBM or Zmax1 is a molecule that binds to, or that inhibits binding of a molecule to HBM to a greater or lesser extent than to Zmaxl, and wherein the molecule involved in lipid regulation is a molecule that binds to, or that inhibits binding of a molecule to HBM to a greater or lesser extent than to Zmaxl."

Claim 61 is indefinite because it is not clear if "the molecule" (see line 2 of claim 61) and "the molecule involved in lipid regulation" (lines 4-5 of claim 61) are the same or different molecules. Based on claim 1 it would appear that both "the molecule" and "the molecule

involved in lipid regulation" were the same molecule. However, if they are the same molecule, it is unclear why claim 61 would recite essentially the same limitation twice; that limitation being: the molecule/the molecule involved in lipid regulation "is a molecule that binds to, or that inhibits binding of a molecule to HBM to a greater or lesser extent than to Zmax1."

Appropriate correction is required.

Claim Rejections - 35 USC § 101 and 112, 1st paragraph combined

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

It is noted that the previous Office Action contained a rejection of record under 35 USC 101 and 35 USC 112, which Applicants have responded to. In view of Applicants arguments, the Examiner has modified the rejections in order to more clearly set forth the Examiner's position. For instance, the instant rejections more clearly set forth the distinction between the rejection under 35 USC 101 and the rejection under 35 USC 112, first paragraph. Applicants' arguments as they pertain to the new rejections are found at the end of this Action.

Claims 1, 2, 6, 7 and 48-61 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility.

The instant claims are drawn to a method for identifying a molecule involved in lipid regulation comprising identifying a molecule that binds to, or that inhibits the binding of a molecule to, HBM or Zmax1 (see claim 1); as well as a method for identification of candidate

molecules involved in lipid regulation by identifying molecules that bind to the nucleic acid of Zmax1 (SEQ ID NO: 1), or a polymorphism of Table 4 except one specific polymorphism, or an HBM nucleic acid having SEQ ID NO: 2 (see claim 6)

When considering the utility of the instant claims, the issue is not merely whether Zmax1 and HBM have utility in and of themselves, but whether the claimed methods of identifying *molecules involved in lipid regulation* have utility under 35 U.S.C. § 101. To be clear, the issue is whether or not identifying molecules involved in lipid regulation has credible, substantial and specific or well-established utility.

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification. The specification clearly asserts that the claimed methods have utility for identifying molecules involved in lipid regulation. The specification, as well as the prior art indicate, indicates that lipids are involved in many important biological processes. Furthermore, it is recognized that an aberrant serum lipid levels is associated with disease. For instance, aberrantly high levels of serum lipids has been associated with atherosclerosis and other various diseases. Since identifying molecules associated with disease is credible, the asserted utility for the claims is credible.

The second issue is whether substantial and specific utilities are disclosed in the specification. As indicated above, the specification must assert substantial AND specific utility for the claimed methods. With respect to "specific" utility, MPEP 2107.01 states,

> A "specific utility" is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. Office personnel should distinguish between situations where an applicant has disclosed a specific use for or application of the invention and situations where the applicant merely indicates that

> the invention may prove useful without identifying with specificity why it is considered useful. For example, indicating that a compound may be useful in treating unspecified disorders, or that the compound has "useful biological" properties, would not be sufficient to define a specific utility for the compound. Similarly, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed. Contrast the situation where an applicant discloses a specific biological activity and reasonably correlates that activity to a disease condition. Assertions falling within the latter category are sufficient to identify a specific utility for the invention. Assertions that fall in the former category are insufficient to define a specific utility for the invention, especially if the assertion takes the form of a general statement that makes it clear that a "useful" invention may arise from what has been disclosed by the applicant. Knapp v. Anderson, 477 F.2d 588, 177 USPQ 688 (CCPA 1973).

The specification asserts that the method has utility for identifying molecules involved in lipid regulation. However, term "involved" is vague and does not assert any specific way that the molecules are in lipid regulation. Therefore, identifying molecules that are merely "involved" in lipid regulation without indicating how they are specifically "involved" does not constitute a specific assertion of utility for the claimed method. Furthermore, the term "lipid regulation" is vague and encompasses regulating lipids at all possible levels including regulating lipid production, lipid metabolism, and any other process associated with lipids. As such, "lipid regulation" is a very broad term and encompasses many different biologically and biochemically distinct processes. For instance, one general process encompassed by the term "lipid regulation" is regulating serum lipid levels in a subject.

The regulation of serum lipid levels is recognized in the art as a very complex process that involves not one single factor, but many different factors including diet as well as the function of many different genes. For instance, Ye et al. (Am. J. Clin. Nutr. 2000; Vol. 72 (Suppl), pages 1275S-1284S; previously cited) teaches that genes influence quantitative

variations in plasma lipoprotein concentrations (see abstract). Specifically, Ye reviews a number of DNA sequence polymorphisms (specifically, polymorphisms in the genes encoding ApoA-I, ApoA-IV, ApoB, ApoC-III, ApoE, LPL, CETP, LCAT, and LDL receptor) which are thought to be involved in plasma lipid regulation. Therefore, Ye teaches that regulating serum lipid levels is a complex process that involves many different biological and biochemical factors and processes including diet as well as the activity of at least 9 specific gene products.

Therefore, it is clear that "lipid regulation" is not limited to a single process but encompasses the involvement of many different biological and biochemical factors and processes. As such, the assertion that the method has utility for identifying molecules involved in lipid regulation is not a specific utility.

It is acknowledged that the specification asserts that Zmax1 and HBM are members of the LDL receptor family, based on sequence similarity alone. The specification also asserts that HBM and Zmax1 are "involved in lipid regulation". However, the specification does not disclose how Zmax1 and HBM are specifically involved in lipid regulation.

With respect to "substantial" utility, MPEP 2107.01 states,

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities": ...
>
> (C) A method of assaying for or identifying a material that itself has no specific and/or substantial utility;

In the instant case, the claimed invention is considered a substantial utility because additional experimentation would be required in order to determine that the identified molecules are actually involved in lipid regulation including the identifying the process/processes of lipid regulation which the molecule is involved in.

The last consideration is whether there is a well-established utility for the claimed invention. The specification and relevant art do not appear to disclose any "well-established" established utilities for the claimed method of identifying molecules involved in lipid regulation using Zmax1 and HBM.

Regarding the involvement of HBM in lipid regulation, the specification discloses that biochemical tests were performed to measure the serum levels of various lipid containing molecules and precursors in affected and unaffected HBM family members to test whether HBM affects lipid regulation (see Example 3, starting at p. 125). The specification discloses that HDL levels are "generally higher in affected males than unaffected males" (see p. 126, line 21-27). However, this appears to be contradictory to data in the art. Specifically, Zabaglia (1998, previously cited) teaches that HDL levels showed an inverse correlation to bone mass in postmenopausal women to a very high degree of statistical significance, indicating that as bone mass increases HDL decreases (while the specification indicates males having high bone mass had increased HDL levels). The only apparent differences between to two data sets is that the specification was analyzing HDL levels in men with high bone mass while Zabaglia was analyzing HDL levels in postmenopausal woman. It is not clear why the association of HBM with HDL is not consistent between the two groups, bringing into question association of HBM with lipid regulation.

Regarding Zmax1's involvement in lipid regulation, there does not appear to be any data presented indicating the any particular lipid profile with Zmax1. The basis of Zmax1 involvement in lipid regulation appears to be based on the sequence similarity of Zmax1 with LDL-receptors and the similarity to HBM.

In conclusion, the claimed invention must be supported by a specific and substantial asserted utility or a well-established utility. The claimed invention is drawn to method of identifying molecules involved in lipid regulation using HBM and Zmax1. As indicated above, the assertion that the methods are useful for identifying molecules that are merely "involved" in "lipid regulation" does not constitute a specific utility for the claimed invention, nor are they substantial utilities as additional experimentation would be required to complete the claimed method. Also, there are no well-established utilities identified for the claimed method. Therefore, the rejection is proper.

Claims 1, 2, 6, 7 and 48-61 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6, 7 and 48-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a written description rejection**.

The instant claims encompass a molecule that inhibits the binding of another molecule (i.e., a second molecule) to HBM or Zmax1. Therefore, the claims encompass inhibiting the binding of the second molecule to HBM or Zmax1 wherein the second molecule can be any molecule that binds to HBM or Zmax1. It is noted that the claims do not set forth the conditions under which the molecule binds to HBM or Zmax1; therefore, the claims encompass molecules which bind to HBM or Zmax1 under any conditions. As such, the claims encompass a genus of molecules that comprises an indefinite number of species molecules. Considering the claims encompass any molecule which binds HBM or Zmax1 under any conditions (as indicated above), the genus encompasses possibly thousands of different molecules, including molecules that have yet to be identified.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

With respect to the molecules that bind Zmax1/HBM encompassed by the claims, the specification only discloses that Zmax1 and HBM "interact with several proteins such as ApoE" (see p. 115). The specification does not disclose any other molecules which bind to Zmax1 or HBM. The specification does not identify any common structures critical to the common function of all species encompassed by the claims (i.e., no structure-function relationship has been disclosed). Furthermore, there are no species molecules found in the prior art.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the specification has proper disclosure of only one molecule that binds to HBM or Zmax1: ApoE. The specification does not meet the written description provision of 35 U.S.C. §112, first paragraph for the entire claimed genus. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6, 7 and 48-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a method for identifying molecules that are involved in lipid regulation by identifying molecules that bind to, or inhibit the binding of another molecule to Zmax1 or HBM. Therefore the nature of the invention is a biological assay to identify molecules that have an effect on lipid regulation wherein said molecules exert their effect either directly or indirectly through Zmax1 or HBM.

The breadth of the claims

The claims are very broad. For instance, the claims encompass identifying molecules that inhibit the binding of a second molecule to Zmax1 or HBM. The second molecule can be any molecule that binds to Zmax1 or HBM. The claims also encompass identifying a molecule that is merely involved in any aspect of lipid regulation. It is pointed out that the claims and specification do not indicate what effect binding of the molecule to Zmax1/HBM would have on lipid regulation. That is, it is not clear from the specification if a molecule identified in the process would be a molecule that increased lipid levels, decreased lipid levels, or even which specific lipids the molecule would effect.

The unpredictability of the art and the state of the prior art

The art of record clearly indicates that lipid regulation is a complex process that involves the action of many different genes as well as other factors such as diet. Specifically, Ye et al. (Am. J. Clin. Nutr. 2000; Vol. 72 (Suppl), pages 1275S-1284S; previously cited) teaches that genes influence quantitative variations in plasma lipoprotein concentrations (see abstract). Specifically, with respect to plasma lipid levels, Ye reviews a number of DNA sequence polymorphisms (specifically, polymorphisms in the genes encoding ApoA-I, ApoA-IV, ApoB, ApoC-III, ApoE, LPL, CETP, LCAT, and LDL receptor) which are thought to be involved in plasma lipid regulation. Therefore, Ye teaches that regulating serum lipid levels is a complex process that involves many different biological and biochemical factors and processes including diet as well as the activity of at least 9 specific gene products.

Therefore, it is clear that "lipid regulation" is not limited to a single process but encompasses the involvement of many different biological and biochemical factors and processes.

Additionally, in order for the method to be able to identify molecules involved in lipid regulation, it is imperative that HBM and Zmax1 are specifically involved lipid regulation. The specification discloses that HBM and Zmax1 are LDL-receptor family members, based on sequences similarity to known LDL-receptors as well as the association of the HBM polymorphism with a particular lipid profile. There is no disclosure in the specification which indicates either HBM or Zmax1 is a functional LDL receptor that is directly involved in lipid regulation.

Furthermore, the relevant art at the time of filing recognized that LDL-receptors could be involved in functions other than lipid regulation. For instance, Willnow et al. (Nature Cell Biol.; Vol. 1, October 1999, pages E157-E162) teaches,

> "Lipoprotein receptors used to be viewed simply as the means by which cells were supplied with lipids for energy production and membrane synthesis. This perception has now changed dramatically. Megalin, a member of the low density lipoprotein receptor gene family, turns out to mediate the endocytic uptake of retinoids and steroids, thus helping to regulate their biological function. Other members of this receptor family interact with cytosolic signaling proteins, giving this evolutionary ancient family of receptors and entirely unexpected new role as transducers of extracellular signals." (See abstract, emphasis added).

Therefore, the prior art teaches that LDL-receptors (which appellants assert includes Zmax1 and HBM) can be involved in processes other than lipid regulation, such as endocytic uptake of retinoids and steroids. Since the LDL receptor is known to be involved in processes other than lipid metabolism, one of ordinary skill in the art would not be able to associate Zmax1 with LDL regulation based on sequence similarity alone.

In view of the totality of the prior art, it is clear that a mere observation that HBM and Zmax1 are associated with lipid regulation and that they are members of the LDL receptor family of proteins is not sufficient to establish that HBM and Zmax1 are directly involved in lipid regulation, which is required in order for the claimed methods to have utility and to be fully enabled.

Working Examples and Guidance in the Specification

With respect to "inhibiting a molecule that binds to HBM or Zmax1" (i.e. the second molecule of the claims) it is noted that the specification only identifies one specific molecule (ApoE) which binds to Zmax1 or HBM.

The specification asserts that Zmax1 and HBM are LDL-receptor family members involved in lipid regulation. The specification asserts that Zmax1 is involved in lipid regulation based on alignments alone. The specification also asserts that HBM is involved in lipid regulation based on sequence similarity as well as the association of the HBM polymorphism with a particular lipid profile. For example, Example 3 in the specification discloses,

> "Since Zmax1 has similarity to the LDL receptor family of genes, it may be involved in lipid metabolism. However, others have reported that lipid profile variables did not show significant association with bone mass and could not be used as indicators for bone mineral density (Zabaglia et al., "An exploratory study of association between lipid profile and bone mineral density in menopausal women in a Campinas reference hospital," Cad. Saude Publica 14: 779-86 (1998)). (Emphasis added)

> "To test whether the HBM gene was involved in lipid regulation, biochemical tests were performed to measure serum level of various lipid containing molecules or precursors in affected and unaffected HBM family members to test whether the HBM mutation in the Zmax1 gene effects lipid metabolism... The results obtained were statistically significant: (1) Triglyceride levels were generally lower in affected individuals than in unaffected individuals, and (2) very low density lipoprotein (VLDL) levels were generally lower in affected individuals than in unaffected individuals. Additionally, the following comparisons approached statistical significance (p=0.06): (1) high density lipoprotein (HDL) levels were higher in affected males than in unaffected males, and (2) the ratio of low density lipoprotein (LDL) to high density lipoprotein (HDL) was generally higher in affected males than in unaffected males." (See p. 126, lines 4-27).

Here, Applicants indicate the Zmax1 has "similarity" to the LDL receptor family of genes, but it is not clear exactly how similar Zmax1 is to the LDL receptors. Applicants acknowledge that the prior art had not made a connection between lipid metabolism and bone mineral density. In this Example, Applicants try to associate the HBM gene with lipid metabolism by evaluating the serum levels of some lipid containing molecules in individuals with and without HBM. The only statistically significant data disclosed indicates the individuals having the HBM polymorphism also have generally lower triglycerides levels and generally lower VLDL levels compared to individuals without HBM.

In contrast to the above disclosure, Zabaglia (1998, previously cited) teaches that HDL levels showed an inverse correlation to bone mass in postmenopausal women to a very high degree of statistical significance, indicating that as bone mass increases HDL decreases (while the specification indicates males having high bone mass had increased HDL levels). The only apparent differences between to two data sets is that the specification was analyzing HDL levels in men with high bone mass and Zabaglia was analyzing 1HDL levels in postmenopausic woman. It is not clear why the association of HBM with HDL is not consistent between the two groups, bringing into question association of HBM with lipid regulation.

The specification does not provide any working examples wherein the claimed method was used to positively identify a molecule involved in lipid regulation.

Quantity of Experimentation

In order to practice the claimed invention to its full scope, additional experimentation would be required in order to first identify the molecules that bind to Zamx1 or HBM (i.e., the second molecules of the claims). Furthermore, once these molecules were identified, additional further experimentation would be required in order to determine which of the molecules actually had an effect on lipid regulation in a subject.

Furthermore, additional experimentation would be required in order to first establish that HBM and Zmax1 are involved in lipid regulation. This would additional experimentation to identify which biochemical process/processes of lipid regulation HBM and Zmax1 are involved in as well as identify how Zmax1 and HBM were specifically "involved" in lipid regulation.

Level of the skill in the art

The level of the skill in the art required to practice the claimed method is deemed to be high.

Conclusion

Considering the nature of the invention, the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the limited amount of working examples and guidance provided, and the high degree of skill required to practice the invention, it is concluded that the specification does not provide an enabling disclosure for the instant claims. Therefore, additional experimentation is required before one of skill in the art could make and use the claimed invention as indicated. The amount of additional experimentation required to perform the broadly claimed invention is undue.

Response to Arguments

Applicant's arguments filed 11/22/04 have been fully considered but they are not persuasive, as they pertain to the instant rejections.

As indicated above, the previous Office Action contained a rejection of record under 35 USC 101 and 35 USC 112, which Applicants have responded to. In view of Applicants arguments, the Examiner has modified the rejections in order to more clearly set forth the Examiner's position. For instance, the instant rejections more clearly set forth the distinction between the rejection under 35 USC 101 and the rejection under 35 USC 112, first paragraph.

It is noted that applicants maintain that the rejections of claims under 35 USC 101 are based entirely on the rejection under 35 USC 101. Applicants assert that the rejection under 35

U.S.C. 112 stands or falls with the rejection under 35 USC 101, as no separate lack of enablement rejection was set forth that was not linked with a finding of lack of utility.

In response, a separate rejection under 35 USC 112, first paragraph has been set forth for the reasons indicated herein. As such, the rejections under 35 USC 101 and 112 do not stand or fall together and should be addressed separately. It is noted that all of applicants arguments are directed to the rejection of claims under 35 USC 101.

With respect to the rejection of claims under 35 USC 101, applicants argue that the Office must show that the claimed invention lacks practical utility, and must provide evidence sufficient to show that the statement of asserted utility would be considered false by one of ordinary skill in the art.

It is noted that Applicants arguments are with respect to the *credibility* of the asserted utility. To be clear, the Examiner does not question the credibility of the asserted utility. Therefore, applicants' arguments with respect to the *credibility* of the asserted utility are moot. The issue, as set forth herein, is whether or not the asserted utility constitutes a specific and substantial utility using the criteria indicated in MPEP 2107.1, as indicated above.

With respect to the whether or not the asserted utility has "substantial" utility, applicants assert that the MPEP states that screening assays "have a clear, specific and unquestionable utility (e.g., they are useful in screening compounds).

In response, it is respectfully pointed out that MPEP 2107.01 (I: Specific and Substantial requirements) states (as indicated above),

> A method of assaying for or identifying a material that itself has no specific and/or substantial utility;

In the instant case, the claimed method is a method of assaying for or identifying a molecule that itself has no specific utility because further experimentation would be required to establish the specific utility of the molecule. Therefore, the method does not have substantial utility.

Applicants also argue that the post filing evidence also supports the asserted utility, such as the results of knocking out the LRP5 gene in mice (see Magoori et al. and Fujino et al.).

In response, it is respectfully pointed out that Magoori does teach a mouse that has been engineered such that it does not have a functional LRP5 gene (i.e., an LRP5 Knock-out mouse) as well as an LRP5:ApoE double knock-out mouse. Magoori clearly teaches that the LRP5 knock-out mouse "had no significant effect on plasma cholesterol levels" (see abstract), and the asserted effect was only found in the LRP5:ApoE double knockout mice. As such, one cannot conclude from the teachings of Magoori that LRP5 is directly involved in lipid regulation. Fujino also teaches that LRP5 knock-out mice have increased plasma cholesterol levels when feed a high-fat diet. It is pointed out that neither Magoori nor Fujino indicate how LRP5 is specifically involved in lipid regulation. Furthermore, it is pointed out that LRP5 does not appear to be identical to HBM/Zmax1,(Applicants appear to acknowledge this by indicating that LRP5 is a different variant of Zmax1 (see p. 8 of Applicants response). Since LRP5 and Zmax1 and HBM are not identical it is quite possible that the have very different functions bringing into question the relevancy of the LRP5 data.

Applicants also argue that MPEP 2108.03 (III) indicates that utility is a low hurdle and a small degree of utility is sufficient.

In response, the credibility of the asserted utility is accepted by the Examiner, the utility rejection is based on the lack of specific and substantial utility as indicated above.

The Applicants' assert that the publications of Johnson et al. and Little et al. show that a single genetic locus is responsible for the phenotypes measured in this kindred. Furthermore, using a mouse genetic model, Fujino et al. and Magoori et al. have clearly shown that a different variant of Zmax1 (the of LRP5 null allele), has a dramatic consequence on lipid levels. Together these data are more than correlative but rather direct evidence of a cause and effect on lipid levels dependent on the inherited Zmax1 allele.

With respect to the teachings of Little and Johnson it is respectfully pointed out that the references do not teach that the single genetic locus responsible for the phenotype is the Zmax1 gene or the HBM gene. In fact, a "gene locus" as identified by Little and Johnson is not a single gene, but rather a chromosomal locus comprising several genes. Furthermore, Fujino and Magoori were previously addressed. Therefore, the references do not indicate that the claimed method has a specific and substantial utility.

With respect to Applicants argument against the Ye et al. reference (p. 8-9), the Ye reference has been used in the instant rejection to indicate that the process of "lipid regulation" is a complex multi-factorial process which supports the position that the claimed method does not have specific and substantial utility.

With respect to Applicants argument against the Willnow et al. reference (p.9-10), applicants argue that in view of the data of Example 3 and of the indicated references, the asserted functions of Zmax1 and HBM are not in doubt. Applicants also state, "An artisan of ordinary skill would certainly not conclude that the asserted utility is false." In response, the

Examiner does not contend that the asserted utility is false, only that it is not specific and substantial. Furthermore, Willnow is now cited in the enablement rejection to indicate that LDL receptors can be involved in functions other than lipid regulation, and is not intended to indicate that the asserted utility is false.

With respect to the data disclosed in the specification and in the art of record, applicants argue that the credibility of the asserted utility is supported by the data (p. 11)

It is acknowledged that the asserted utility is credible. The indicated data does not indicate that asserted utility is specific and substantial for the reasons indicated above.

Applicants contend that the Office has not seemed to consider the post filing art submitted. Applicants specifically refer to Magoori, Fujino, Parhami, Pinals et al. The references have been fully considered. Magoori, and Fujino have been addressed previously. With respect to Parhami and Pinals, the references merely indicate that there is evidence of a link between osteoporosis and cardiovascular disease. Evidence of a link between osteoporosis and cardiovascular disease does not establish a specific and credible utility for the claimed invention since a mere link between osteoporosis and cardiovascular disease does not indicate that the claimed method is specific and substantial.

Therefore, the instant rejections are proper.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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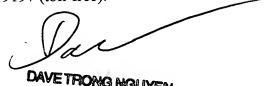

Jon Eric Angell
Art Unit 1635